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EDITORIAL COMMENT

Assessing the Prognostic Value of Coronary Computed Tomography Angiography*

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Computed tomography (CT) imaging of the coronary arteries is challenging. The coronary vessels are small, and they move very rapidly, so that tremendously high spatial and temporal resolution are necessary to obtain sharp images of the coronary tree. The first CT system successfully used to visualize the coronary arteries was the electron beam tomography (EBT) scanner, which became available in the late 1980s and early 1990s and was also called "ultrafast CT" because of its ability to acquire images at unprecedented speed. With an exposure time of 100 ms/image, the EBT scanner allowed faster imaging than most multidetector CT systems in use today, but limitations included a spatial resolution much lower than that of current CT scanners, rather high image noise, and a long overall image acquisition time (patients typically had to hold their breath for more than 30 s).

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The main application of EBT was the detection and quantification of coronary artery calcification. In addition, EBT first demonstrated the ability of CT imaging to obtain "noninvasive coronary angiograms" after injection of a contrast agent. In the mid 1990s, this new development received tremendous interest and fueled the surprisingly rapid evolution of CT technology, much of which was driven by the desire to improve the ability of CT to visualize the coronary arteries. Today, 64-slice CT systems, which allow rather stable imaging of the coronary vessels, are widely available. Coronary computed tomography angiography (CTA) is considered an "appropriate" clinical tool in selected situations, including ruling out coronary stenoses in symptomatic patients with intermediate likelihood of coronary artery disease (1). Although numerous comparisons of CT imaging to invasive angiography have been published and demonstrate a high accuracy for the detection of "obstructive" coronary artery lesions, very little is known about the prognostic implications of coronary CTA.

The study presented by Ostrom et al. (2) in this issue of the *Journal* provides data concerning the prognostic value of contrast-enhanced CT visualization of the coronary arteries. The investigators followed up 2,538 patients studied by contrast-enhanced EBT for up to 15 years. Based on their large number of patients, complete follow-up, and long observation period, they are able to demonstrate that the presence of obstructive and nonobstructive coronary artery lesions seen in contrast-enhanced EBT is predictive of mortality above and beyond traditional risk factors. Demonstration of lesions is also a better predictor than the mere assessment of coronary calcification. The severity of coronary lesions and the extent of disease (e.g., 1 affected vessel vs. several affected vessels) were associated with mortality rates. After adjustment for risk factors and coronary calcium score, patients with obstructive lesions seen in EBT angiography had an approximately 2-fold risk of death as compared to patients without detectable atherosclerosis. Interestingly, noncalcified, nonstenotic plaque was found to be predictive only if its extent was substantial: only patients who had all 3 vessels affected had an increased mortality.

Obviously, the study by Ostrom et al. (2) has some limitations—for example, it is unclear how many patients were symptomatic and what treatment was initiated based on the EBT results—but it does provide very interesting early data concerning the prognostic implications of coronary plaque detected in contrast-enhanced CT imaging. As is typically the case with new and exciting research results, the study answers some questions, but also raises many new ones, some of which are outlined below.

Symptomatic patients or asymptomatic individuals? In my opinion, it is important to carefully distinguish 2 clinical scenarios. The first scenario is the use of coronary CTA for symptomatic patients. For some subgroups of patients who do not have a high likelihood of coronary artery stenoses, this is currently considered appropriate (1). Clinically, the aim of CT will be ruling out coronary artery stenoses to avoid invasive catheterization. Prognostic studies are needed to clarify whether it is safe to replace invasive angiography by CT, and also to determine whether patients in whom CT rules out the presence of obstructive lesions (thus avoiding invasive angiography) but demonstrates the presence of nonobstructive plaque are at higher risk of cardiac events than are patients with entirely normal coronary arteries on CT. This determination is important in order to make appropriate recommendations regarding risk modification in such patients. The study by Ostrom et al. (2) provides some data in this respect.

The second scenario is that of the asymptomatic patient for whom coronary CTA is performed for the sole purpose

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of "risk stratification" in a primary prevention context. This is quite a different setting. Most patients in the study by Ostrom et al. (2) probably had symptoms, and similarly, the few other available studies that have investigated prognostic implications of coronary CTA were all conducted in patients who were largely symptomatic (3–7). It is important not to use results obtained from such patient groups to justify coronary CT "screening" of asymptomatic patients. Pretest likelihoods and future event risks are substantially lower, and the balance between test benefit and associated risks (and costs) may be profoundly different from that of symptomatic patients. The use of contrast-enhanced coronary CTA for risk stratification for asymptomatic patients is currently considered an "inappropriate" application (1), and in my opinion, the study by Ostrom et al. (2) will not change that.

Did technology matter? The study by Ostrom et al. (2) was conducted using EBT, which is not widely available anymore. The EBT data collected by Ostrom et al. (2) are extremely valuable because they allow a long follow-up period, but EBT has meanwhile been replaced by multidetector computed tomography (MDCT), which has higher spatial resolution and, in general, better image quality than EBT. However, this does not mean that detection of plaque by MDCT is easy. Data sets of impeccable quality are required to assess the presence or absence of nonobstructive plaque, and even in expert hands, neither sensitivity nor specificity is perfect (8). With adequate image quality, however, it should be expected that more noncalcified plaque will be identified in MDCT as compared to EBT—a double-edged sword. On the one hand, it will make it less likely that a patient with a future event will be missed by MDCT. On the other hand, I suspect that even more plaque may be detected by MDCT, and that may lead to a larger number of patients being placed in a "high risk" category. Again, it is important to keep in mind that only plaque in all 3 vessels was predictive of future events in the study by Ostrom et al. (2). Small, localized plaques have so far not been tied to an increased event risk.

Would the mere detection of plaque be enough? Ostrom et al. (2) used a "yes/no" model to assess the presence of obstructive and nonobstructive coronary lesions by CT. Most likely, that will not be sufficient in the future (Fig. 1). Not all "nonobstructive lesions" are alike—for example, they may be small, confined to the vessel wall, and predominantly calcified, or they can be large, positively remodelled, and largely noncalcified. However, as noncalcified plaque is observed very frequently by contrast-enhanced coronary CTA (more than one-half of all patients in the study by Ostrom et al. [2], and about 30% of patients in a different study [9]), merely evaluating the presence of plaque may place too many individuals in a "high-risk" category, with the consequence of (expensive) risk modification treatment as well as considerable emotional stress. Efforts will have to be undertaken to identify characteristics that are associated with increased risk of future events, whether this may be global features (such as plaque volume), specific aspects of a

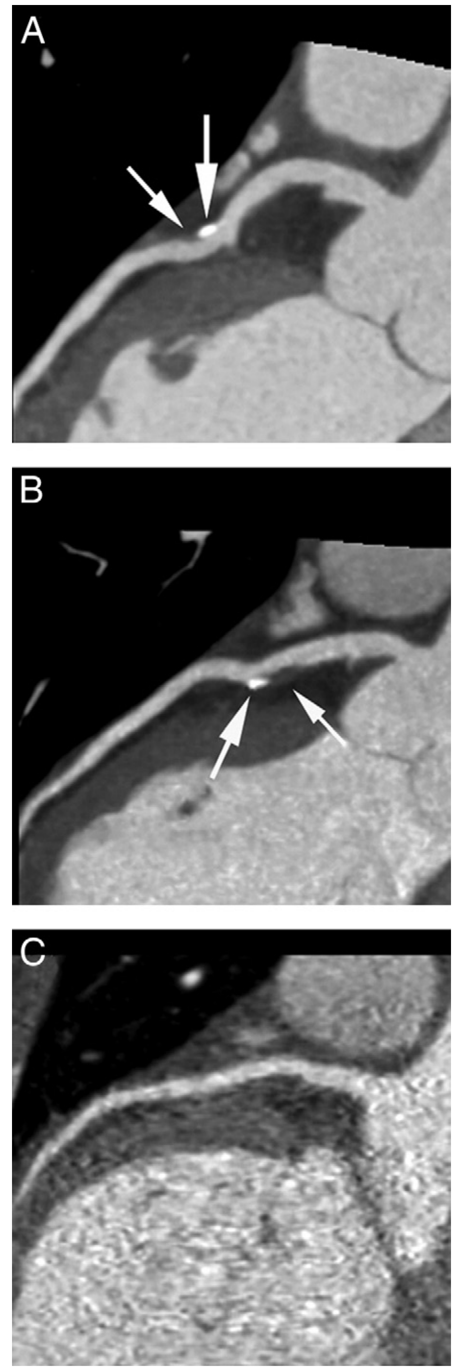

Figure 1 **Visualization of Proximal and Mid LAD by Contrast-Enhanced MDCT in 3 Patients**

Visualization of the proximal artery and mid left anterior descending coronary artery (LAD) by contrast-enhanced multidetector computed tomography (MDCT) in 3 different patients. **(A)** Visualization of a small calcified plaque **(large arrow)** along with some noncalcified plaque **(small arrow)** in the mid left anterior descending coronary artery. **(B)** While nominally this patient also demonstrates calcified **(large arrow)** and noncalcified, nonobstructive plaque **(small arrow)**, the lesion has different characteristics as compared with **A**. The noncalcified plaque component is substantially larger, and the lesion displays pronounced positive remodeling. Potentially, this lesion may be more "vulnerable" than the lesion in **A**. **(C)** Not in all cases is image quality high enough to reliably rule in or rule out small noncalcified plaque. Although coronary stenoses can be ruled out, image noise prevents assessing the presence of noncalcified plaque in this low-dose image.

given plaque (such as remodeling), or a combination of both (10). A small, noncalcified plaque may actually be pretty harmless and in fact, the absence of substantial amounts of noncalcified plaque may at some point allow "downstaging" of patients concerning their risk, but future research will need to address this issue.

How much can we afford to spend? Even when leaving the economic implications of CT angiography for risk stratification completely aside, this test comes at a cost: the injection of contrast and the associated radiation exposure place CTA in a completely different category as compared to, for example, coronary calcium imaging. Low radiation dose protocols are becoming increasingly available for CTA, but flawless image quality is necessary to be able to assess the presence or absence of plaque with a reasonable degree of certainty. Studies performed at very low dose or affected by other sorts of artifacts may be sufficient to rule out the presence of coronary stenosis, but not necessarily to visualize or even characterize plaque (Fig. 1). Contrast and radiation risks have to be assessed very carefully if ever considering the use of CTA in primary prevention settings.

In summary, the paper by Ostrom et al. (2) is helpful and very welcome as it provides more data on the prognostic implications of coronary visualization using CT techniques. It contains the very reassuring message that the absence of stenosis and nonobstructive plaque is associated with a good prognosis, even in a patient population that was most likely largely symptomatic. However, the results do not justify the use of CTA as a screening tool for asymptomatic, primary prevention patients.

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